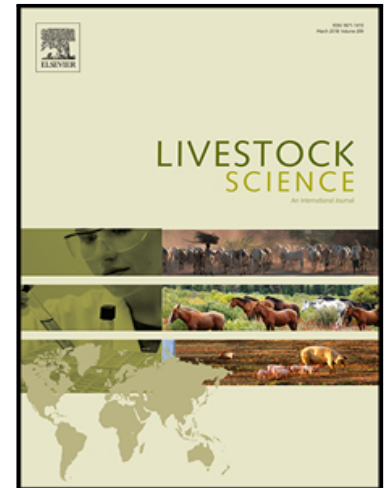


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Highlights

- Genotype-environment interaction study for growth traits in composite beef cattle
- Evidence of genotype-environment interaction was found in birth and weaning weight
- This study showed a change in SNP effects across different pre-natal environments

**Genomic evaluation of genotype by prenatal nutritional environment interaction for
maternal traits in a composite beef cattle breed**

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Abstract

Genes interact with both pre- and postnatal environments potentially affecting several important traits in beef cattle. The main objective of this study was to evaluate the existence of genotype by prenatal nutritional environment interaction using genomic information in growth traits, birth weight (BW), weaning weight (WW) and yearling weight (YW) in a composite beef cattle breed (50% Red Angus, 25% Charolais, and 25% Tarentaise). Dams were randomly assigned to be fed in two levels of harvested supplemental feed from Dec to March of each year that were expected to result in adequate (ADEQ) or marginal (MARG; ~ 61% of the supplemental feed provided by ADEQ) levels of protein based on average quality and availability of winter forage. This design resulted in two prenatal nutritional environments: MARG and ADEQ. A total of 3,020 records were used in a two-trait model treating each environment as a different trait. Genetic parameters for all three traits were estimated using genomic information. The direct genetic correlations between environment ADEQ and MARG were 0.97, 0.97 and 0.99 for BW, WW and YW respectively. On the other hand, the maternal genetic correlations between the two environments were 0.62, 0.41 and 0.73 for BW, WW and YW respectively. Furthermore, direct and maternal genomic estimated breeding values (GEBVs) using single step genomic BLUP were computed and the solutions of SNP markers were back solved from the resulting GEBVs to compare genomic regions associated with the two environments. The present study demonstrated the existence of maternal genetic by prenatal nutritional environment interaction especially for BW and WW in beef cattle.

Key words: Prenatal environment, SNP, genetic correlation, genotype-environment interaction

Introduction

Economically important traits are controlled by both genetic and environmental factors and often their interaction. Moreover, beef cattle are required to perform in different environments and management practices. Numerous studies have shown that genotype by environment (GxE) interaction impacts the performance of animals. However, little research has been specifically conducted on the extent of the interaction of genotype with the prenatal “*in utero*” environment. It is increasingly becoming apparent that maternal environment has long-term effects on the offspring through fetal programming (Nathanielsz et al., 2007).

In livestock populations, several studies have shown that nutrition during gestation is linked to the progeny’s growth and performance (Benyshek et al., 2004; Zambrano et al., 2005; Bieswal et al., 2006; Ford et al., 2007). Zhu et al. (2006) conducted a study on the long term effects of fetal programming on offspring and showed that nutrient restriction during midgestation resulted in offspring with decreased lean to fat ratio compared with their counterparts. Funston et al. (2010) showed that maternal nutrition during fetal development affects conceptus growth and the performance of the offspring. Recently, Roberts et al. (2016) showed that nutritional management strategies used during gestation and development impacts the lifetime productivity of beef heifers. Here, we explore the interaction of genotype and prenatal nutritional environment and its effect on genetic merit of the animal.

To model genotype by environment interaction in animal agriculture, two approaches are widely used: multi-trait and reaction norm models. The multi-trait model is used when the environments are categorical, considering each record for a given phenotype in a specific environment as different and assuming potential genetic correlation (Hayes et al., 2003; Mulder

and Bijma, 2005; Williams et al., 2012; Raidan et al., 2015). The second method is using a reaction norm model which requires a continuous environmental variable. This approach estimates the animal genetic merit across the environmental variable (Ravagnolo and Misztal, 2000; Pegolo et al., 2011; Cardoso and Tempelman, 2012; Hammami et al., 2015; Fennewald et al., 2017) .

The objective of this study is to evaluate the existence and the extent of genotype by prenatal nutritional environment on maternal traits (birth weight, weaning weight and yearling weight) through a multi-trait model using genomic information and also evaluate the change of SNP marker effects across the different nutritional environments.

Materials and Methods

Data

The data used in this study consisted of a total of 3,020 records collected on animals from a composite beef cattle breed (50% Red Angus, 25% Charolais and 25% Tarentaise) born between 2002 and 2011 at USDA-ARS, Fort Keogh Livestock and Range Research Laboratory, Miles City, MT. The 3,020 animals had both phenotypic and genotypic information. The prenatal environments were constructed by randomly assigning cows to be fed two levels of harvested supplemental feed from December to March of each year. First level is adequate winter supplemental feed (ADEQ) according to NRC nutrient requirements and second is marginal supplemental feed (MARG) which is approximately 61% of the supplemental feed provided by ADEQ. Additional information concerning breed and experimental design are available in Newman et al. (1993a, 1993b) and Roberts et al. (2016), respectively. The pedigree file consisted of 5374 animals including 128 sires and 1723 dams. The phenotypes considered in this study are

birth weight, weaning weight and yearling weight. Summary statistics of the phenotypes used in the study is presented in table 1.

Animals were genotyped using a mixture of low density SNP 3k panel, 7k panel, 9k panel and Illumina Bovine50k (Illumina, San Diego, CA). Animals genotyped with low density panels were imputed to the 50K SNP panel using FImpute software (Sargolzaei et al., 2011) where population and pedigree information were both considered. The average allelic R^2 was 0.94 which indicates high imputation accuracy of the missing genotypes.

Quality control using SVS software (Golden Helix, Inc., Bozeman, 2010) was performed excluding SNP markers with minor allele frequency less than 0.05 and SNPs with Call Rate (CR_{SNP}) < 0.90 and Fisher's exact test P -value for Hardy-Weinberg Equilibrium (HWE) $< 1 \times 10^{-5}$. After quality control, the total number of remaining SNP markers for the analysis was 41,694.

Statistical Analysis

The model used to evaluate the extent of genotype by environment interaction is a two-trait model considering each observation of a specific trait in a different environment as a different trait. In beef cattle genetic evaluations, BW, WW and YW are usually fit together in a three-trait model, however since the data is small and to minimize the computing cost, the traits were fit separately. All analyses were carried out using the BLUPF90 software package (Misztal et al., 2002). The two-trait model in matrix notation, applied in this study is the following:

$$\begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} X_1 & 0 \\ 0 & X_2 \end{bmatrix} \begin{bmatrix} b_1 \\ b_2 \end{bmatrix} + \begin{bmatrix} Z_1 & 0 \\ 0 & Z_2 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \end{bmatrix} + \begin{bmatrix} W_1 & 0 \\ 0 & W_2 \end{bmatrix} \begin{bmatrix} m_1 \\ m_2 \end{bmatrix} + \begin{bmatrix} Q_1 & 0 \\ 0 & Q_2 \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \end{bmatrix},$$

where \mathbf{y}_1 and \mathbf{y}_2 are the vectors of phenotype records classified by maternal winter supplementation environments ADEQ and MARG, respectively, \mathbf{b}_1 and \mathbf{b}_2 are vectors of the solutions of fixed effects in environments ADEQ and MARG which included sex effect and contemporary group effect (year and age-of-dam subclasses), \mathbf{a}_1 and \mathbf{a}_2 are vectors of genomic breeding values in environments ADEQ and MARG, \mathbf{m}_1 and \mathbf{m}_2 are the vectors of maternal genomic breeding values in environments ADEQ and MARG, \mathbf{p}_1 and \mathbf{p}_2 are vectors of random maternal permanent environmental effects in environments ADEQ and MARG, $\mathbf{X}_1, \mathbf{X}_2, \mathbf{Z}_1, \mathbf{Z}_2, \mathbf{W}_1, \mathbf{W}_2, \mathbf{Q}_1$ and \mathbf{Q}_2 are incidence matrices that relate phenotypes with respective effects and \mathbf{e}_1 and \mathbf{e}_2 are vectors of random residuals for ADEQ and MARG. No animal had observations in more than one environment. The random residuals $\begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix}$ are assumed to be normally distributed with mean 0 and variance co-variance $\mathbf{I} \otimes \mathbf{R}$, where $\mathbf{R} = \begin{bmatrix} \sigma_{11}^2 & \sigma_{12} \\ \sigma_{12} & \sigma_{22}^2 \end{bmatrix}$. The genetic variance co-variance structure is given by $\mathbf{H} \otimes \mathbf{T}$ where $\mathbf{T} =$

$$\begin{bmatrix} \sigma_{a1}^2 & \sigma_{a1 \ a2} & \sigma_{a1 \ m1} & \sigma_{a1 \ m2} \\ \cdot & \sigma_{a2}^2 & \sigma_{a2 \ m1} & \sigma_{a2 \ m2} \\ \cdot & \cdot & \sigma_{m1}^2 & \sigma_{m1 \ m2} \\ \cdot & \cdot & \cdot & \sigma_{m2}^2 \end{bmatrix} \text{ and } \mathbf{H} \text{ is the genotyped and non-genotyped relationship}$$

matrix constructed following (Aguilar et al., 2010) and the genomic relationship matrix of genotyped animals was constructed following (VanRaden, 2008).

First variance components were estimated using AIREMLF90 (Misztal et al., 2002) and second genomic estimated breeding values (GEBV) using the BLUPF90 software package (Misztal et al., 2002) were also estimated. After obtaining direct and maternal GEBVs, SNP effects were back solved following (Wang et al., 2012). First, the correlations between different sets of SNP marker effects derived from maternal genetic effects were calculated to investigate the change of

SNP effects between the two environments. Second, the percentage of the genetic variance accounted by fixed windows of 20 SNP markers were also computed to detect the relevant chromosome regions related to the traits. The following equation (Wang et al., 2012) was used to estimate the percentage of genetic variance explained by a specific SNP:

$$v_i = 100 \times \left(2p_i q_i \alpha_i^2 / \sum_{i=1}^{nsnp} 2p_i q_i \alpha_i^2 \right),$$

where p_i and q_i are the allele frequencies for the i^{th} SNP calculated based on the dataset, α_i^2 is the SNP effect estimated from the genomic breeding values.

Results and Discussion

Table 2 shows the estimates of the genetic parameters of the traits in the two environments using the multi-trait model. The heritabilities and the direct and maternal genetic correlations between the two environments (ADEQ and MARG) are presented in Table 3. The estimates of heritabilities for the three traits were within the reported estimates in the literature. For BW, the direct genetic heritabilities were 0.46 and 0.42 in environments MARG and ADEQ, respectively. Bullock et al. (1993) reported a birth weight heritability of 0.49 in a Hereford cattle herd. In other breeds, Winder et al. (1990) reported a heritability of 0.46. The heritabilities for weaning weight were 0.37 and 0.34 in environments MARG and ADEQ, respectively. These estimates were also within the reported heritabilities in the literature (Massey and Benyshek, 1981; Iwaisaki et al., 2005). For yearling weight, heritability estimates were 0.24 and 0.23 MARG and ADEQ, respectively which are in concordance with previously reported estimates. The heritabilities were higher in MARG for all traits which could be due to differences in genetic expression caused by the nutritional environment dams were subjected to. Interestingly, both the

additive genetic variance and the maternal genetic variance were higher in the MARG environment across the traits. For example, the additive genetic variance for BW was 14.12 ± 2.03 and 11.09 ± 1.78 and the maternal genetic variance was 5.13 ± 0.63 and 3.53 ± 0.49 for MARG and ADEQ respectively. This is expected since improved environments may mask the true genetic potential of animals because the phenotypic expression is confounded with the environment effects. Furthermore, this difference in genetic variation could be due to the presence of better-adapted dams to the MARG condition and some dams better adapted to ADEQ condition. The genetic correlations between direct and maternal effects were around -0.08, -0.37, and -0.06 for BW, WW, and YW, respectively. For BW, the correlation is lower than estimates reported in the literature (Crews Jr, 2006; Mujibi and Crews Jr, 2009) which could be due to the small dataset used in this study. For WW, the correlation is within the estimates in the literature (Lee et al., 1997). It is reasonable to deduce that in this population cows with poor maternal ability would wean heavier calves. This genetic antagonism is hard to explain and varying biological explanations have been reported on the negative direct-maternal genetic correlation of WW (Moore et al., 1991; Lee, 1999). Finally, the maternal genetic correlation between the two environments was higher for YW compared to BW and WW which is expected since maternal genetic effect does not have a large effect on this trait. These low direct-maternal genetic correlations do not necessarily mean that pre-natal nutrition does not have an effect on the progeny, the genetic correlations between the two environments are more indicative of a genotype by prenatal interaction.

A genetic correlation between a trait measured in different environments of value less than 0.8 is an indicator of genotype by environment interaction (Robertson, 1959). The direct

genetic correlations between the two environments were all above 0.8, on the other hand the maternal genetic correlations were 0.62, 0.41 and 0.73 for BW, WW and YW, respectively. Therefore, the results suggest a genotype by environment interaction effect especially for BW and WW affecting the maternal genetic component. The results were expected given the maternal influence on birth weight and weaning weight. Figure 1 shows the direct estimated genomic breeding values (GEBV) of 10 random animals in environments ADEQ and MARG using the multi-trait model. Little or no change was observed in the ranking of animals and the magnitude of the direct GEBVs across the two environments suggesting no effect of genotype by environment interaction. On the other hand, the maternal estimated genomic breeding values showed a change in magnitude and a re-ranking of animals for BW, WW and YW across the two environments (Figure 2). Therefore, it is apparent that genotype by environment interaction is affecting BW and WW. Interestingly, in some instances, lower feed input (MARG) resulted in a higher maternal GEBV compared to higher input (ADEQ) as seen in YW (Figure 2). This could be due to a maternal genetic component adapted to lower feed input environments.

The maternal genetic effect of BW showed a genotype by prenatal nutritional environment interaction. This finding is supported by several studies that reported significant effects on birth weight caused by altering the feeding of heifers and cows during the second and third trimester (Freetly et al., 2000; Cafe et al., 2006). Protein supplementation has been suggested to influence birthweight during the last trimester of pregnancy (Holland and Odde, 1992). Moreover, fetal muscle development is affected by maternal nutrition more than other organs (Close and Pettigrew, 1990) and a decrease in nutrients can cause a reduction in muscle fibers (Zhu et al., 2004). Contradictory results have been reported in the literature on the effects of protein supplementation on birth weight. A study by Martin et al. (2006) showed that dams

provided protein supplements did not differ from non-supplemented dams in terms of calves birth weights. On the other hand, a study by Larson et al. (2009) suggests that protein supplementation during the last trimester may increase birth weight in beef cattle. From the resulting maternal genomic estimated breeding values, some animals in the MARG group had higher values than animals in the ADEQ group as for yearling weight. Therefore, greater level of winter supplementation during the last trimester did not always increase the genetic merit of the offspring.

The maternal genetic effect of WW has also shown a genotype by environment interaction. This could be explained by the change in lactational performance of the dams due to the winter supplementation restriction.

Genome-wide association study

Table 4 presents the correlations of the 10, 100, 1000 largest and all SNP marker effects for the maternal genetic effect in ADEQ with MARG. The correlation of the 10 top largest SNP effects for BW was 0.84, 0.87 for top 100 SNP, 0.92 for top 1000 and 0.98 for all SNP markers (Table 4). Similar trend was observed for WW, on the other hand a small change in correlations was seen for YW. From the results, SNP markers with high effects are not conserved across different environments. In dairy cattle, Tsuruta et al. (2015) found SNP makers with high effects to be consistent across different environments. However, in their study, SNP effects were computed from direct genomic estimated breeding values in each environment separately without accounting for genotype by environment interaction.

To further examine the change of SNP effects across the environments, both direct and maternal effects were used to identify SNP markers associated with the traits in the two environments. For BW maternal effect in both ADEQ and MARG environments, the SNP

window explaining the highest percentage of genetic variance was found on 24Mb BTA14 (Figure 3). This SNP window explained 2.41% of the maternal genetic variance in environment ADEQ and 3.15% in MARG. This region of the genome harbors several genes and QTLs affecting growth and carcass traits. Kneeland et al. (2004) reported three QTLs on BTA14 in a composite beef cattle breed associated with birth weight. An important gene in this region related to mothering ability is DGAT1. This gene is associated with milk production (Thaller et al., 2003) but also with fat production in dairy and beef cattle (Wu et al., 2012; Tait Jr et al., 2014). In addition, Lee et al. (2013) conducted a genome wide association study of carcass traits in Hanwoo breed and detected a significant QTL on BTA14 at 24.3-25.4 Mb associated with carcass weight. Several genes are in this region such as *PENK*, *PLAG1-CHCHD7*, *LYN*, *IMPAD1*, *SDR16C5*, *LYPLA1*, *MRPL15*, *FAM110B*, *UBXN2B*. The *PLAG1-CHCHD7* has been reported to be associated with growth traits, bovine stature, residual feed intake and carcass traits in both Indicine and Taurus breeds (Lee et al., 2013; de Oliveira Silva et al., 2017). Karim et al. (2011) reported the same region of the genome detected in this study on bovine chromosome 14 which mapped two QTLs to the *PLAG1-CHCHD7*. Moreover, the *LYPLA*, and *LYN* genes have also been reported to be associated with feed intake and growth traits in beef cattle (Lindholm-Perry et al., 2012; Magalhães et al., 2016). The second highest SNP window for BW in MARG was located on BTA27 and explained 0.74% but only 0.22% in ADEQ. On the other hand, the second highest SNP window in ADEQ was located on BTA13 and explained 1.15% of genetic variance and 0.13% in MARG. A recent genome wide association of maternal genetic effect on birth weight did not show any overlapping significant regions with our study (Yin and König, 2019). They reported two significant SNPs on BTA4 and BTA19. For maternal effect of WW, the SNP window explaining the highest genetic variance (1.11%) was located on BTA24 at

11Mb. One potential candidate gene ATP9B is located at that region. This gene is involved in transport of glucose, bile salts and organic acids, metal ions and amine compounds and ion channel transport (Takatsu et al., 2011). This change in SNP effects across the two environments was also noticeable for YW for maternal effects (Figure 4, Figure 5). For GWAS of direct genetic effects, SNP effects have not changed across the two environments except for BW in BTA14 as shown in Figure S1, S2 and S3.

Conclusions

The present study shows the existence of a genotype by prenatal nutritional environment interaction for maternally influenced growth traits in beef cattle. Moreover, these results warrant the need to account for genotype by environmental interaction in national genetic evaluations. Genomic information has the potential to remedy this problem, since SNP marker effects could be estimated for different environments.

Conflict of Interest

None

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Table 1. Summary statistics for birth weight (BW), weaning weight (WW) and yearling weight (YW)

Trait	Environment	n	mean	SD
BW	MARG	1481	34.31	5.64
	ADEQ	1531	35.34	5.63
WW	MARG	1483	207.19	30.64
	ADEQ	1530	208.53	30.29
YW	MARG	1474	342.46	76.18
	ADEQ	1529	336.27	72.92

Table 2. Genetic parameters for birth weight (BW), weaning weight (WW) and yearling weight (YW) in MARG and ADEQ prenatal environments using two-trait model

	BW		WW		YW	
	MARG	ADEQ	MARG	ADEQ	MARG	ADEQ
σ_a^2	14.12 (2.03)	11.09 (1.78)	158.81 (14.27)	132.63 (16.42)	282.14 (25.08)	271.60 (24.11)
σ_m^2	5.13 (0.63)	3.53 (0.49)	59.71 (6.31)	50.14 (7.50)	79.37 (8.26)	76.05 (8.04)
σ_e^2	2.87 (0.55)	4.19 (1.02)	157.16 (15.82)	158.33 (14.90)	745.23 (69.01)	743.81 (77.13)
σ_p^2	8.31 (1.70)	7.21 (1.89)	47.15 (5.60)	46.36 (7.01)	58.72 (9.19)	56.91 (6.77)
σ_{am}	-0.47 (0.02)	-0.51 (0.03)	-40.34 (3.25)	-30.15 (4.03)	-10.61 (2.13)	-9.03 (2.41)

σ_a^2 = direct additive genetic variance; σ_m^2 = maternal additive genetic variance; σ_e^2 = residual variance; σ_p^2 = permanent environmental variance; σ_{am} = co-variance between direct and maternal additive genetic effects

Table 3. Direct and maternal genetic heritabilities and correlations for birth weight (BW), weaning weight (WW) and yearling weight (YW) in MARG and ADEQ prenatal environments using a multi-trait model

	BW		WW		YW	
	MARG	ADEQ	MARG	ADEQ	MARG	ADEQ
h_a^2	0.46 (0.04)	0.42 (0.03)	0.37 (0.02)	0.34 (0.01)	0.24 (0.02)	0.23 (0.03)
h_m^2	0.16 (0.01)	0.13 (0.01)	0.14 (0.01)	0.12 (0.01)	0.07 (0.03)	0.06 (0.04)
r_a	0.97 (0.01)		0.97 (0.01)		0.99 (0.01)	
r_m	0.62 (0.04)		0.41 (0.03)		0.73 (0.06)	

h_a^2 = heritability for direct additive effects; h_m^2 = heritability for maternal effects; r_a = direct genetic correlation between MARG and ADEQ; r_m = maternal genetic correlation between MARG and ADEQ

Table 4. Correlation of SNP effects of maternal genetic effect between MARG and ADEQ prenatal environments for birth weight (BW), weaning weight (WW) and yearling weight (YW)

Number of SNP	BW	WW	YW
10	0.84	0.82	0.93
100	0.87	0.84	0.94
1000	0.92	0.90	0.97
All SNP	0.98	0.97	0.98

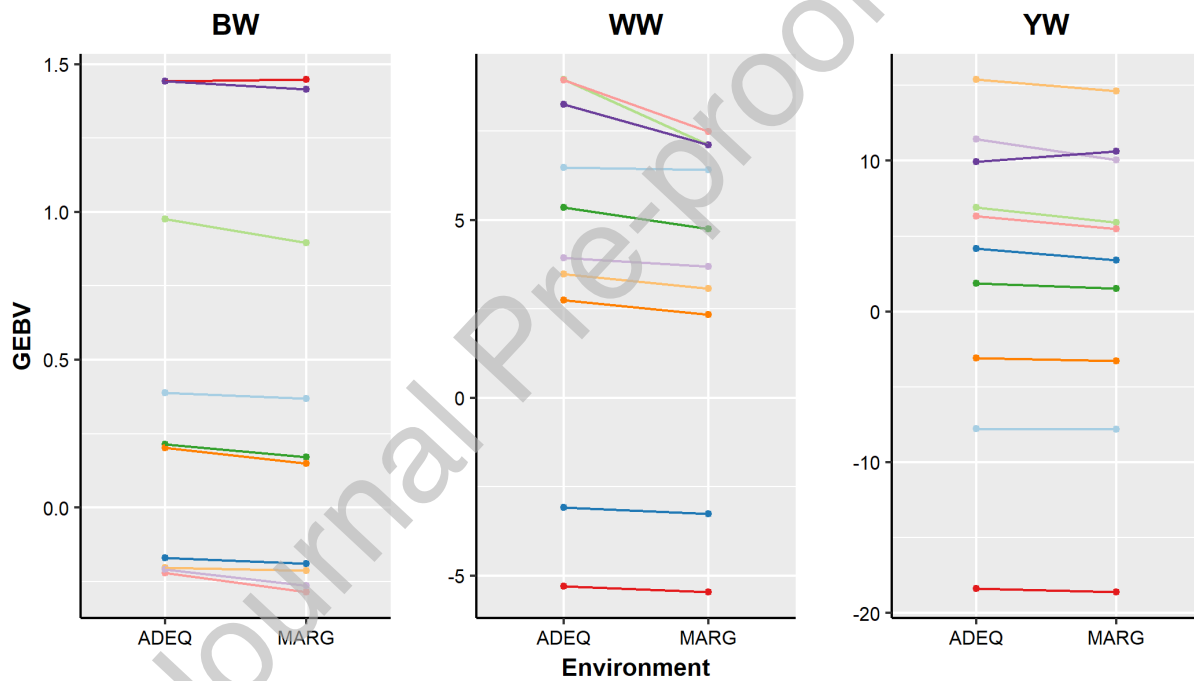


Figure 1. Estimated direct genomic breeding values in for 10 random animals for birthweight (BW), weaning weight (WW) and yearling weight (YW) in different prenatal environments using a multi-trait model.

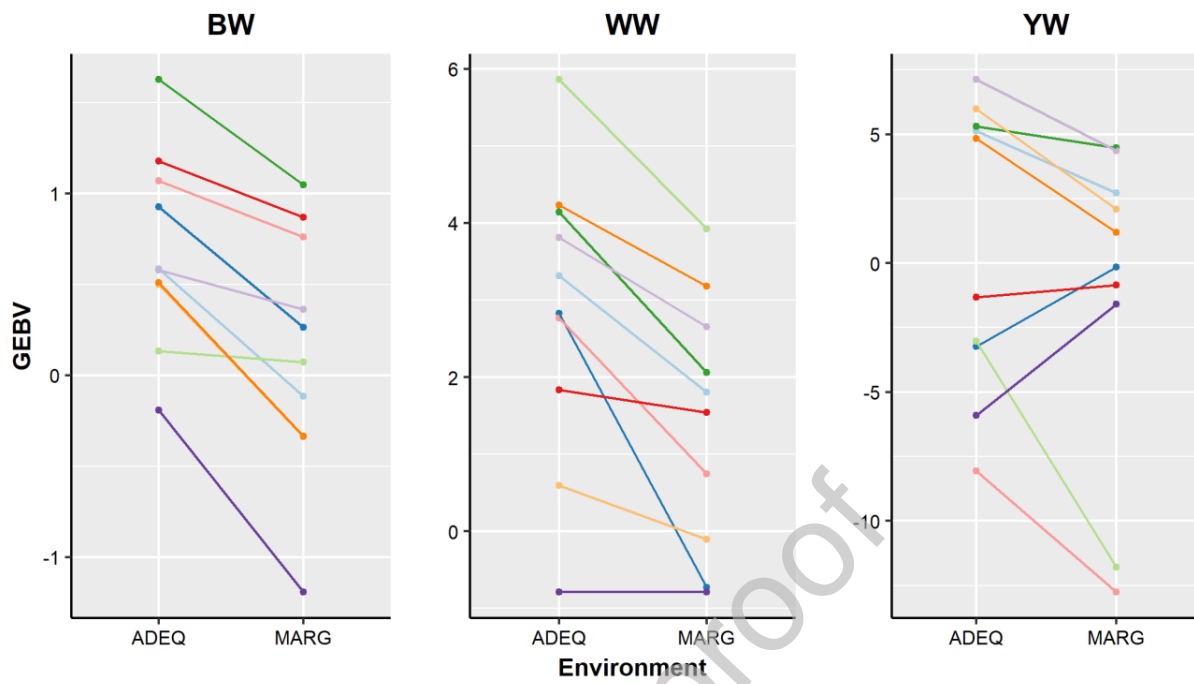


Figure 2. Estimated maternal genomic breeding values in for 10 random animals for birth weight (BW), weaning weight (WW) and yearling weight (YW)) in different prenatal environments using a multi-trait model.

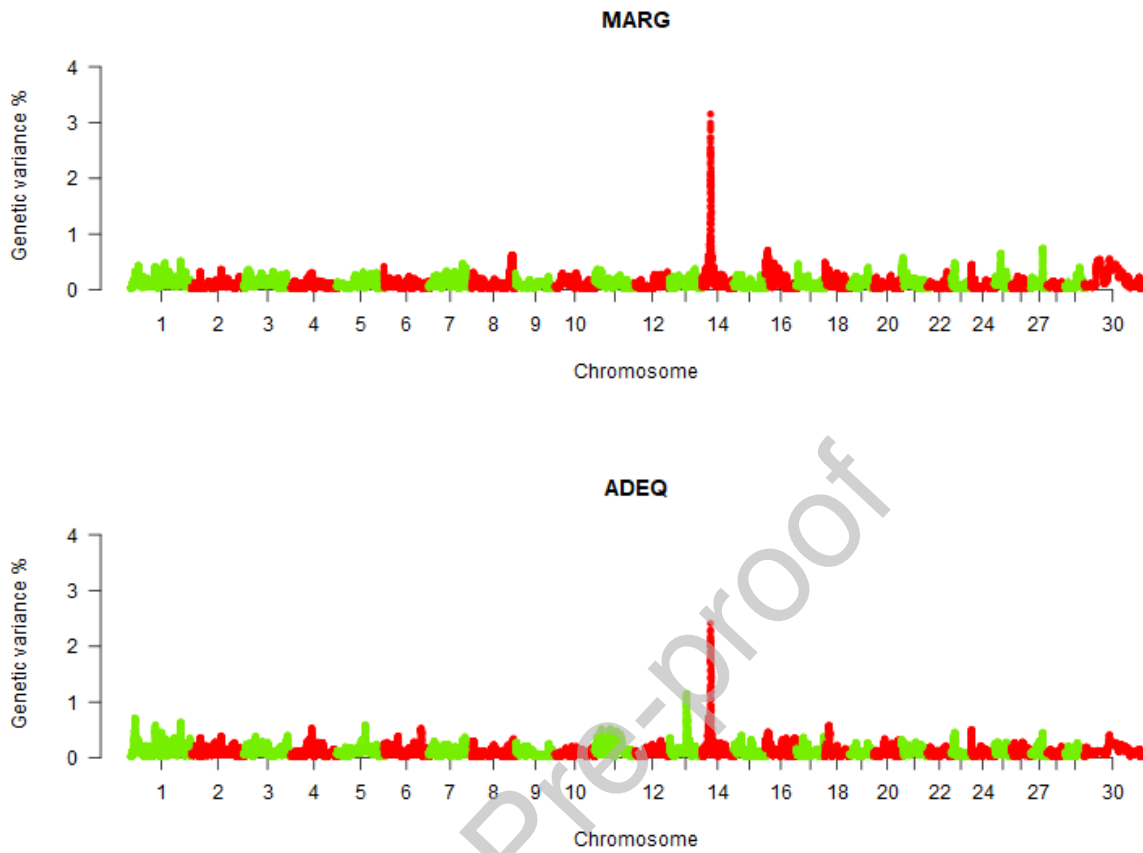


Figure 3. Manhattan plot for maternal effect for birth weight (BW) in ADEQ and MARG prenatal environments.

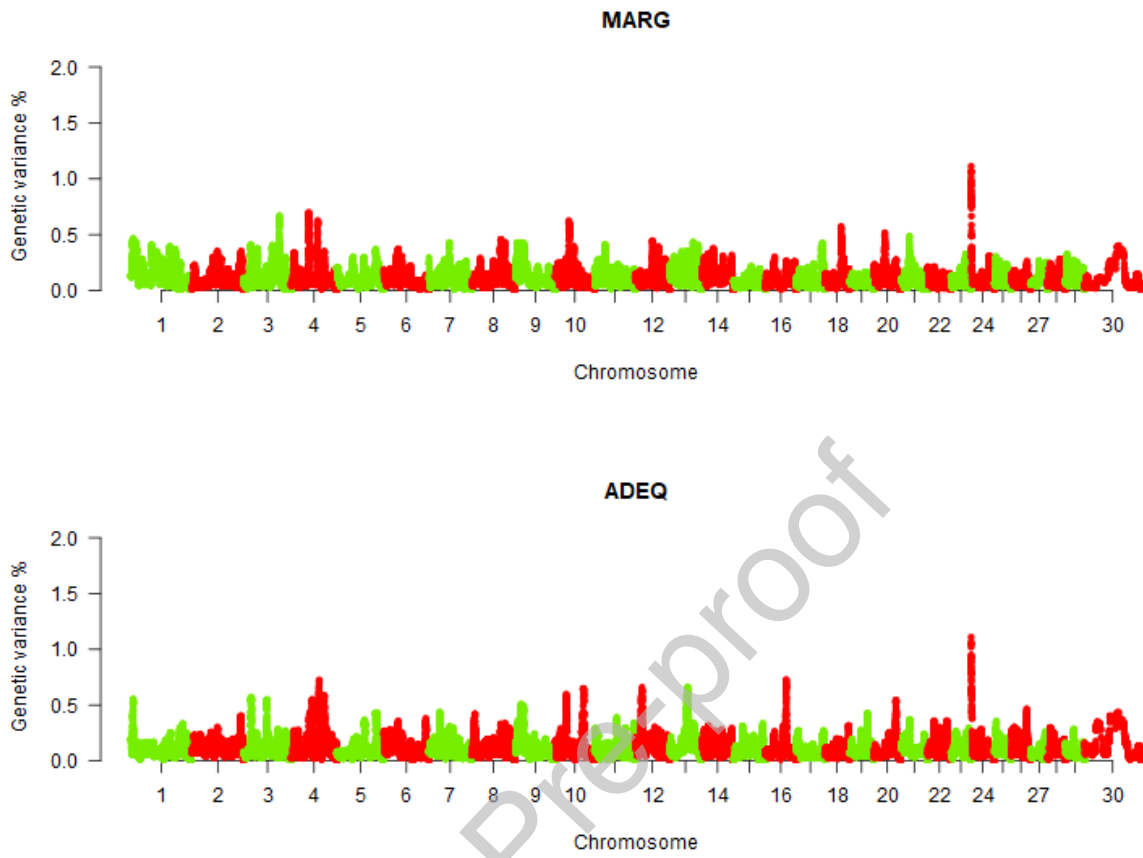


Figure 4. Manhattan plot for maternal effect for weaning weight (WW) in ADEQ and MARG prenatal environments.

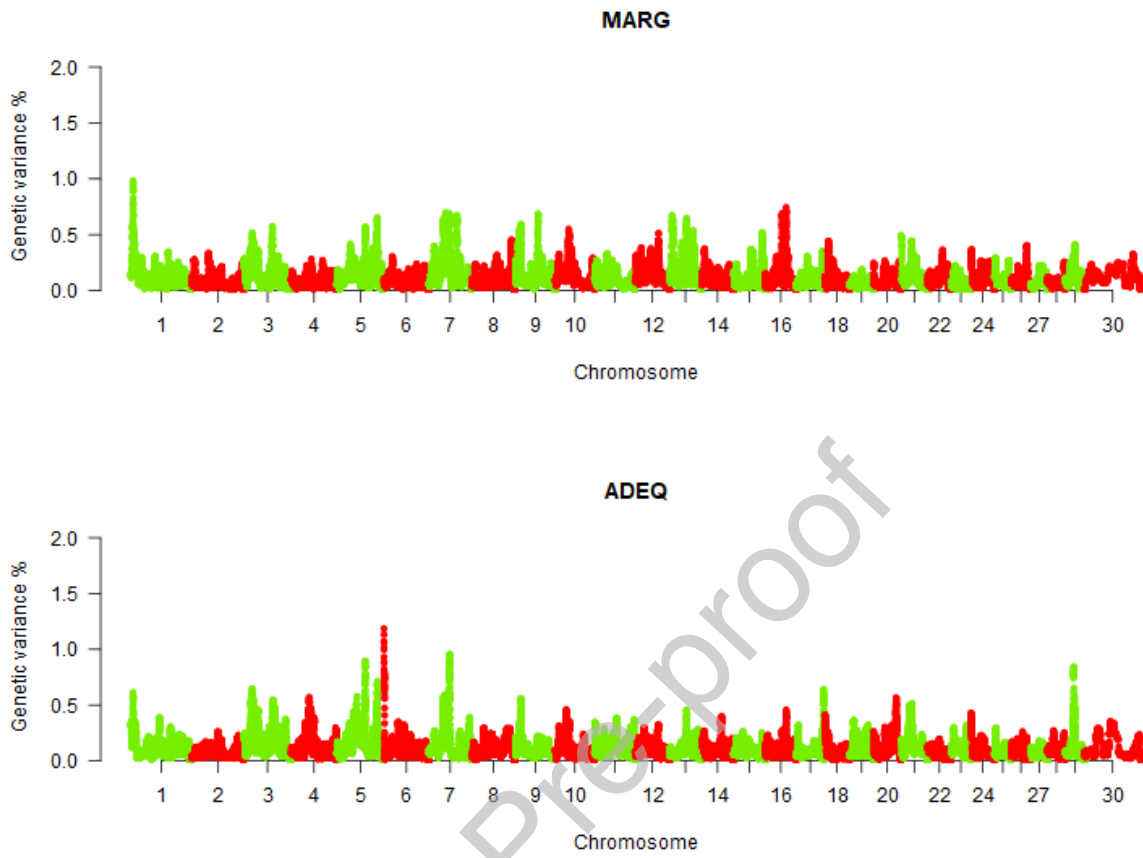


Figure 5. Manhattan plot for maternal effect for yearling weight (YW) in ADEQ and MARG prenatal environments.